



ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain

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ABSTRACT

Introduction: An Excel[®] (Microsoft Corporation) model was adapted to estimate the short-term (1-year) cost effectiveness of insulin detemir (IDet) versus neutral protamine Hagedorn (NPH) insulin in patients initiating insulin treatment with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in Spain.

Methods: Clinical benefits included the non-severe hypoglycemia rate for T1DM and T2DM, and weight change for T2DM. Three scenarios were included with different hypoglycemia rates estimated on the basis of

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clinical trials and observational studies. Costs, estimated from perspective of the Spanish Public Healthcare System (Euros 2014), included insulin treatment and non-severe hypoglycemia management costs. Non-severe hypoglycemia, defined as a self-managed event, implied the use of extra glucose testing strips and a general practitioner visit during the week following the event for 25% of patients. An average disutility value was associated to non-severe hypoglycemia events and, for T2DM, to one body mass index unit gain to calculate quality-adjusted life years (QALYs).

Results: For the three scenarios a range of 0.025–0.076 QALYs for T1DM and 0.014–0.051 QALYs for T2DM were gained for IDet versus NPH due to non-severe hypoglycemia and weight gain avoidance, in return of an incremental cost of €145–192 for T1DM and €128–206 for T2DM. This resulted in the IDet versus NPH incremental cost-effectiveness ratio (ICER) ranging between €1910/QALY and €7682/QALY for T1DM and €2522/QALY and €15,009/QALY for T2DM.

Conclusion: IDet was a cost-effective alternative to NPH insulin in the first year of treatment of patients with T1DM and patients with T2DM in Spain, with ICERs under the

threshold value commonly accepted in Spain (€30,000/QALY).

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Keywords: Cost-effectiveness analysis; Insulin detemir; Type 1 diabetes mellitus (T1DM); Type 2 diabetes mellitus (T2DM); Spain

INTRODUCTION

Diabetes mellitus is a group of heterogeneous metabolic disorders with the common features of hyperglycemia and glucose intolerance, which affects about 10.8% of the Spanish population [1]. In patients with type 1 diabetes mellitus (T1DM), insulin endogenous secretion is impaired, while patients with type 2 diabetes mellitus (T2DM), which represent about 90% of diabetes cases, do not respond to endogenous insulin properly [2]. Therefore, insulin therapy is indicated for all patients with T1DM as they are completely dependent on exogenous insulin; however, only patients with T2DM who are unable to achieve adequate glycemic control by other measures (exercise, diet, and/or other antidiabetic agents) will receive insulin treatment [3].

The main treatment goal in people with diabetes is to achieve a normal blood glucose level to reduce the risk of microvascular and macrovascular long-term complications [2]; however, acute hypoglycemia represents the most common adverse event associated with insulin treatment [4] and have a substantial economic and social impact [5]. Therefore, the principle of ‘basal’ insulin use is the optimization of glycemic control, minimizing the risk of hypoglycemia to improve health-related quality-of-life (HRQoL) and adherence to treatment [6].

Either intermediate-acting (neutral protamine Hagedorn [NPH]) or long-acting (insulin glargine or insulin detemir [IDet]) formulations may be used as initial basal therapy aimed to control blood glucose between meals and overnight [6]. Long-acting insulin analogs more accurately mimic the physiological human insulin profile and provide an alternative to human insulins such as NPH insulin [6]. In addition, long-acting insulins are associated with fewer hypoglycemia events and less weight gain than NPH [7, 8]. These improvements lead to better quality-adjusted life years (QALYs) compared with NPH insulin [9, 10].

Hypoglycemia can be classified on the basis of the event management. While severe hypoglycemia requires the assistance from another person, sometimes from a medical professional and even hospital care [11], non-severe hypoglycemia is defined as an episode that can be managed by the patients themselves. Although non-severe hypoglycemic events are easier to manage, they are more common than severe events [12]. Recurrent episodes of non-severe hypoglycemia may cause behavioral changes and cognitive impairment, leading patients to develop fear of hypoglycemia [13], reducing HRQoL, and affecting treatment adherence [13–15]. Furthermore, severe and non-severe hypoglycemia is associated with direct healthcare costs and indirect costs due to productivity loss [11, 16, 17]. Weight gain is also commonly associated with insulin therapy, especially among patients with T2DM [18], and is linked to an increased risk of cardiovascular morbidity and mortality [19].

For these reasons, the importance of controlling hypoglycemia events in the management of both T1DM and T2DM has been recognized in the reimbursement process

in several countries. Insulin analogs with a reduced rate of hypoglycemia and weight gain, like IDet, may provide long- and short-term health benefits with respect to traditional human insulins [20, 21]; however, this clinical benefit and improved quality of life comes with the additional pharmacy costs associated with IDet.

Thus, we aimed to estimate the cost effectiveness of IDet compared with NPH insulin when initiating insulin treatment in patients with T1DM and patients with T2DM using a conservative short-term modeling approach from the perspective of the Spanish National Health System (NHS).

The present study is based on the treatment benefits associated with a reduction in hypoglycemic events and less weight gain as observed in clinical trials and observational studies. Given the short-term design of these studies, a short-term modeling approach is the most conservative option to include clinical data from independent sources and to avoid unrealistic extrapolation derived from long-term horizons. As this kind of cost-effectiveness analysis (CEA) for IDet versus NPH is only available for Scandinavian countries [10, 22], this is the first study, to our knowledge, from the perspective of the Spanish NHS.

METHODS

Cost-Effectiveness Model

A 1-year CEA model was developed in Excel® 2007 (Microsoft Corporation) to compare basal insulin treatment with IDet against NPH insulin for the management of T1DM and T2DM. For the current analysis, input parameters of the model were adapted to the Spanish NHS. The

clinical benefit was defined in terms of QALYs and reflects the effects of hypoglycemic events and weight gain. Only direct health care costs are included (insulins and management of minor hypoglycemic events).

Structure of the Model

The structure of the model is based on two Scandinavian studies: Valentine et al. [10] (T1DM) and Ridderstråle et al. [22] (T2DM). To assess the comparison, two arms are considered, one receiving IDet and one receiving NPH insulin. Each arm is provided with input data obtained from clinical trials [20, 21] and observational studies [23, 24]. As the model was designed to only take into account statistically significant clinical benefits, only the rate of non-severe hypoglycemia for both T1DM and T2DM [10] and the weight change from baseline for T2DM [22] are included in the evaluation. Other clinical parameters, such as severe hypoglycemic events and glycated hemoglobin control were excluded as their differences were found to be not significant. Disutility associated to weight gain and hypoglycemic events is used to estimate QALYs and the incremental cost-effectiveness ratio (ICER; €/QALY) is estimated as the relation between QALYs and costs of one arm versus another.

Study Population

The population consisted in two hypothetical cohorts of patients with either T1DM or T2DM taking up insulin treatment. The number of individuals in the cohort is irrelevant to the result as cost and clinical outcomes are expressed as average yearly costs and rates of event per patient.

Treatments to Compare

One cohort of patients was treated with IDet and the other with NPH. The daily dose was assumed to be 40 IU/day [10], which is the defined daily dose (DDD) indicated by the World Health Organization (WHO) [25].

Time Horizon and Perspective

To estimate the cost-effectiveness of IDet compared to NPH in patients with T1DM and patients with T2DM in Spain, the time horizon considered was one year. The perspective adopted was that of the Spanish NHS.

Clinical Data Inputs

Due to the lack of a study which examines hypoglycemia rates, hypoglycemia IDet/NPH ratios, and weight changes associated to both treatment arms (NPH and IDet for patients with T1DM and patients with T2DM) we have collected clinical data inputs from independent robust sources which are summarized below.

Hypoglycemia Rates

Three scenarios were estimated in which the NPH arm was assigned three different hypoglycemia rates (Table 1). Two scenarios were defined based on data from an observational prospective study conducted in six secondary care diabetes centers in the UK over 9–12 months [23]. The UK Hypoglycemia Study [23] hypothesized that diabetes type and the duration of insulin treatment influenced the risk of hypoglycemia. To test this hypothesis, they explored the epidemiology of hypoglycemia in individuals with diabetes. A total of 383 patients aged 17–75 years were included in three treatment groups for T2DM:

(1) sulfonylurea, (2) insulin for <2 years, and (3) insulin for >5 years, and into two treatment groups for T1DM: (1) insulin for <5 years and (2) insulin for >15 years and asked to self-report all non-severe (self-treated) and severe hypoglycemic episodes (requiring medical assistance). Hypoglycemic episodes were recorded using two complementary methods: Self-reported, when a patient experiences symptoms usually associated with hypoglycemia, or biochemical, reporting all episodes with glucose levels <3.0 mmol/L. The hypoglycemia rates were extracted from self-reported hypoglycemic episodes corresponding to the cohort of patients that recently began insulin treatment. The follow-up period ranged from a mean of 8.8 [standard deviation (SD) 2.6] months in sulfonylurea-treated subjects to 10.3 (SD 3.0) months in longstanding T1DM. As a result, for patients with T1DM treated <5 years a mean of 35.5 [95% confidence interval (CI) 22.8–48.2] events were self-reported, while a mean of 4.08 (95% CI 2.4–5.8) episodes were reported for patients with T2DM treated <2 years. From a cohort with more than 15 years of insulin treatment, a mean of 29.0 (95% CI 16.4–41.8) events for T1DM and 10.2 (95% CI 5.4–15.0) episodes for T2DM were selected.

A more recent observational cross-sectional study carried out in Spain [24] was chosen to estimate the third scenario, describing the frequency of self-reported non-severe and severe hypoglycemic events in patients with T1DM and patients with T2DM. A total of 630 individuals [$n = 294$ (47%) with T1DM and $n = 336$ (53%) with T2DM] aged 15 years or older and receiving insulin were enrolled to fill out a questionnaire survey, and a total of 506 patients completed the four questionnaires comprised in the study. The first questionnaire collected the self-reported frequency of

Table 1 NSH rates assigned to NPH cohort and estimated NSH rates for IDet cohort in patients with T1DM and patients with T2DM

Source	Cohort	NPH NSH rate (NSH/patient year) [95% CI]	Overall hypoglycemia [21] IDet/ NPH RR	Approximate NSH IDet rate (NSH/patient year)
<i>T1DM</i>				
UK Hypoglycemia Study Group (2007) [23]	Insulin < 5 years	35.5 [22.8–48.2]	0.84	$35.5 \times 0.84 = 29.82$
UK Hypoglycemia Study Group (2007) [23]	Insulin > 15 years	29.0 [16.4–41.8]	0.84	$29.0 \times 0.84 = 24.36$
Orozco-Beltrán et al. (2014) [24]	T1DM	88.0	0.84	$88.0 \times 0.84 = 73.92$
<i>T2DM</i>				
UK Hypoglycemia Study Group (2007) [23]	Insulin < 2 years	4.08 [2.4–5.8]	0.52	$4.08 \times 0.52 = 2.12$
UK Hypoglycemia Study Group (2007) [23]	Insulin > 5 years	10.2 [5.4–15.0]	0.52	$10.2 \times 0.52 = 5.30$
Orozco-Beltrán et al. (2014) [24]	T2DM, T2BOT	18.3	0.52	$18.3 \times 0.52 = 9.52$

IDet Insulin detemir, *NPH* Neutral protamine Hagedorn, *NSH* Non-severe hypoglycemia, *RR* Rate ratio, *T1DM* Type 1 diabetes mellitus, *T2BOT* Treated with basal insulin plus oral therapy, *T2DM* Type 2 diabetes mellitus

non-severe and severe hypoglycemia in the previous year, while the other three questionnaires were administered weekly, to record the frequency of non-severe and severe hypoglycemia in the preceding 7 days. From this study, a mean yearly non-severe hypoglycemia rate of 88.0 for T1DM and of 18.3 for T2DM receiving basal-only therapy based on long-acting insulin were selected to feed the model.

Hypoglycemia IDet/NPH Ratios

Lacking a robust source for the non-severe hypoglycemia IDet/NPH ratio, the IDet/NPH rate ratio (RR) for overall hypoglycemic events in patients with T1DM was extracted from a systematic review and meta-analysis study carried out by the Canadian Agency for Drugs and Technologies in Health (CADTH) [21]. The

study aimed to evaluate the clinical efficacy and safety of the long-acting insulin analogs compared with intermediate- and long-acting unmodified human insulins and oral antidiabetic drugs (OADs) for the treatment of T1DM, T2DM, and gestational diabetes [21]. MedLine, Embase, and BIOSIS previews and the Cochrane library were searched for the terms “diabetes,” “long-acting insulin,” and “short-acting insulin analogs,” and filtered by randomized controlled trials (RCTs), over the period of 1990–2007. Outcomes of interest included glycemic control (glycosylated hemoglobin or A1C, fasting plasma glucose), hypoglycemia, body weight, quality of life, patient satisfaction, healthcare utilization, and long-term complications of diabetes. From a meta-analysis of six RCTs (2109 patients), the reduction of non-severe hypoglycemia was

statistically significant when IDet was compared with NPH, with an IDet/NPH overall hypoglycemia RR of 0.84 (95% CI 0.74–0.97).

On the other hand, IDet/NPH RR was estimated at 0.52 (0.44–0.61) for patients with T2DM [20, 22], on the basis of a multicenter, randomized, open-label, 3-arm (morning or evening IDet vs. evening NPH), parallel-group clinical trial [20]. This trial was conducted in 91 centers across Europe and the United States over 20 weeks. It was aimed at comparing the effectiveness and tolerability of IDet administered once daily with those of NPH insulin. Patients eligible for inclusion were adults, with a body mass index (BMI) ≤ 40 kg/m², who had a diagnosis of T2DM of at least 12 months, and were receiving ≥ 1 OAD but were insulin naïve. A subanalysis comparing IDet clinical outcomes by time of administration was also conducted. A total of 504 patients were enrolled (285 male, 219 female); patients were randomly assigned in a 1:1:1 ratio to receive either IDet before breakfast ($n = 168$); IDet in the evening ($n = 170$), or NPH insulin in the evening ($n = 166$). When evening administration of IDet was compared with NPH, the hypoglycemic RR obtained was 0.52 for patients with T2DM.

Considering the rate of non-severe hypoglycemia in the NPH arm and the overall hypoglycemia IDet/NPH RR in T1DM [21] and T2DM [20], the rate of approximate non-severe hypoglycemia episodes for patients with T1DM and patients with T2DM who received IDet was calculated by multiplying the respective hypoglycemic rate for patients receiving NPH insulin by the IDet/NPH RR, as reported in Table 1 for both T1DM and T2DM.

Weight

The same IDet versus NPH RCT described above [20] was the source of the IDet versus NPH mean

weight change difference for patients with T2DM. The study reported an increase in body weight following insulin initiation in both evening IDet and NPH insulin groups (0.7 vs. 1.6 kg, respectively) with respect to the baseline, with the mean difference being 0.91 kg ($P < 0.005$) [20].

Source of Costs Data

Only pharmacy and non-severe hypoglycemia management costs were included in the model. Costs were computed from the perspective of the Spanish NHS and are expressed in Euros of the year 2014 [26]. Pharmacy daily costs are detailed in Table 2. Pharmacy costs were reimbursed by the Spanish NHS. IDet cost is discounted by 7.5% (discount in force at the time of the estimation, i.e., September 2014).

Non-severe hypoglycemia management costs were assumed to consist only of the cost of an average of 5.6 extra glucose test strips per event, as it was considered that this would be the only measurable cost of self-managed hypoglycemia [10, 17, 22]. Additionally, it was assumed that 25% of the cohort visits a general practitioner as a consequence of a non-severe hypoglycemic event, as is reported by Brod et al. [17]. The non-severe hypoglycemia management costs are detailed in Table 3.

Utilities

The utility value for symptomatic non-severe hypoglycemia for patients with T1DM and patients with T2DM was -0.0054 , which was calculated by averaging the utility associated to nocturnal (-0.0067) and diurnal (-0.0041) episodes [29].

For patients with T2DM, the utility value assigned for the BMI increment was estimated in -0.0100 per BMI unit increase [30]. To

Table 2 Daily drug costs from the perspective of the Spanish NHS

Drug	Unit cost (€/IU)	Source	DDD	Source	Treatment cost/day
IDet (Levemir [®])	0.0310	[26]	40 IU/day	[25]	€0.0310/IU × 40 IU/day = €1.2408
NPH insulin (Insulatard [®] Flexpen [®])	0.0162	[26]	40 IU/day	[25]	€0.0162/IU × 40 IU/day = €0.6496

DDD Daily defined dose, IDet Insulin detemir, NHS National Health System, NPH Neutral protamine Hagedorn

Table 3 Resource use and cost per NSH event in Spain

Item	Unit cost	Source	Resource use	Treatment cost/NSH
Cost of NSH				
Glycometer strip	€0.4524/strip	[27]	5.600 strips/NSH	€0.4524/strip × 5.600 strips/NSH = €2.5334
GP visit	€9.9600/visit	[28]	1 GP visit for ¼ of patients following the NSH	€9.9600/visit × ¼ visit/NSH = €2.4900
				NSH = €5.0234

GP General practitioner, NSH Non-severe hypoglycemia

estimate the utility value assigned for weight increments, weight changes were transformed in BMI changes multiplying the weight change by 0.346 ($\Delta\text{BMI} = \Delta\text{weight}/[\text{height}^2]$; considering the mean height of the Spanish population is 1.7 m [31], $\Delta\text{BMI} = \Delta\text{weight} \times 0.346$).

Sensitivity Analysis

A one-way sensitivity analysis (OWSA) was performed to assess model uncertainty. The variables were assigned consecutively an upper and a higher value to estimate the resulting ICER in each case. Intervals included in the analysis are detailed in Table 4 for both T1DM and T2DM. The values of ICER obtained with each parameter variation were represented using tornado-type diagrams. Due to the small differences in weight gain between both treatment arms, an additional scenario was

evaluated dismissing the utility loss due to BMI increase.

A probabilistic sensitivity analysis (PSA) with 1000 simulations was also performed to assess model outcome stability when varying all parameters at once, according to suitable probability distribution [22]. Distributions considered for each parameter were: log-normal for hypoglycemia rates and RRs, normal for the weight changes, beta for disutilities, and gamma for hypoglycemia costs and insulin doses. Results were represented using cost-effectiveness acceptability curves and scatterplots.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Table 4 Variables, base-case values, and SA values for T1DM and T2DM

Variable	Description	Source	Treatment	T1DM		T2DM	
				SA value	Base-case value	SA value	Base-case value
RR CI low (CADTH)	NSH IDet/NPH RR CI low value	[21]	NPH IDet	0.74	0.84	0.440	0.520
RR CI high (CADTH)	Hypoglycemia IDet/NPH RR CI high value	[21]	NPH IDet	0.97	0.84	0.610	0.520
QALY disutility (100% daytime hypos)	Disutility value associated to NSH assuming all daytime events	[29]	NPH IDet	−0.0041	−0.0054	−0.0041	−0.0054
QALY disutility (100% nighttime)	Disutility value associated to NSH assuming all nocturnal events	[29]	NPH IDet	−0.0067	−0.0054	−0.0067	−0.0054
Weight difference lower NPH/higher detemir	NPH-detemir weight gain difference CI lower value attributed to either NPH or detemir	[20]	NPH IDet	–	–	−0.10	−0.31
Weight difference higher NPH/lower detemir	NPH-detemir weight gain difference CI higher value attributed to either NPH or detemir	[20]	NPH IDet	–	–	−0.53	−0.31
Cost of minor hypos (−20%)	Cost of NSH event decreased by 20%	Assumption	NPH IDet	€4.02	€5.02	€4.02	€5.02
Cost of minor hypos (+20%)	Cost of NSH event increased by 20%	Assumption	NPH IDet	€6.03	€5.02	€6.03	€5.02
Cost of IDet (−20%)	Unit cost of IDet treatment decreased by 20%	Assumption	NPH IDet	€0.0162	€0.0162	€4.02	€5.02
Cost of IDet (+20%)	Unit cost of IDet treatment increased by 20%	Assumption	NPH IDet	€0.0248	€0.0310	€6.03	€5.02
Cost of NPH (−20%)	Unit cost of NPH treatment decreased by 20%	Assumption	NPH IDet	€0.0162	€0.0162	€0.0162	€0.0162
				€0.0372	€0.0310	€0.0248	€0.0310
				€0.0130	€0.0162	€0.0162	€0.0162
				€0.0310	€0.0310	€0.0372	€0.0310

Table 4 continued

Variable	Description	Source	Treatment	T1DM		T2DM	
				SA value	Base-case value	SA value	Base-case value
Cost of NPH (+20%)	Unit cost of NPH treatment increased by 20%	Assumption	NPH	€0.0195	€0.0162	€0.0130	€0.0162
			IDet	€0.0310	€0.0310	€0.0310	€0.0310

CADTH Canadian Agency for Drugs and Technologies in Health, *CI* Confidence interval, *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *NSH* Non-severe hypoglycemia, *QALY* Quality-adjusted life year, *RR* Rate ratio, *SA* Sensitivity analysis, *T1DM* Type 1 diabetes mellitus, *T2DM* Type 2 diabetes mellitus

RESULTS

Base Case

Due to lower non-severe hypoglycemia rates in patients with T1DM, IDet treatment yields an improvement with respect to NPH insulin ranging between 0.025 and 0.076 QALYs, at an incremental cost between €145 and €192 per patient per year for the three scenarios considered in the base case. Therefore, the ICER for IDet versus NPH insulin was estimated at €1910/QALY to €7682/QALY, depending on the three different hypoglycemia rates considered (Table 5).

For patients with T2DM, IDet was associated with significantly fewer non-severe hypoglycemic episodes and less weight gain compared to NPH insulin, resulting in a 0.014–0.051 QALY gain for the three base-case scenarios, in return of an incremental cost of €128–€206 for the Spanish NHS. Therefore, the IDet versus NPH insulin ICER was estimated at €2522/QALY to €15,009/QALY in Spain, in relation to the three different hypoglycemia rates considered (Table 5).

One-Way Sensitivity Analysis

OWSA was conducted for key input parameters. Overall, results are detailed in Figs. 1 and 2 for T1DM and T2DM, respectively. The variable that has the highest impact on the ICER for T1DM is IDet/NPH hypoglycemia RR, with ICER values varying from €1965/QALY to €36,592/QALY, when varying the IDet/NPH hypoglycemia RR between 0.74 and 0.97. The second variable with the highest impact on ICER is the daily cost of IDet treatment, which makes ICER decrease to €3152/QALY when decreased by 20%, and increase to €9058/QALY when increased by 20%. All other

Table 5 Base-case cost-effectiveness results for patients with T1DM and T2DM in Spain

	Treatment arm	QALYs	Incremental QALYs	Annual cost (€)		Incremental costs (€)	ICER (€/QALY)
				Pharmacy	NSH management		
<i>T1DM</i>							
NSH rate _{NPH} = 29.0	IDet	0.868	0.025	452.89	122.37	575.26	7681.96
	NPH insulin	0.843		237.10	145.68	382.78	
NSH rate _{NPH} = 35.5	IDet	0.839	0.031	452.89	149.80	602.691	6105.08
	NPH insulin	0.808		237.10	178.33	415.436	
NSH rate _{NPH} = 88.0	IDet	0.601	0.076	452.89	370.60	823.49	1909.70
	NPH insulin	0.525		237.10	441.19	678.29	
<i>T2DM</i>							
NSH rate _{NPH} = 4.08	IDet	0.986	0.014	452.89	10.66	463.55	15,008.94
	NPH insulin	0.972		237.10	20.50	257.60	
NSH rate _{NPH} = 10.2	IDet	0.969	0.030	452.89	26.65	479.54	6463.33
	NPH insulin	0.939		237.10	51.24	288.34	
NSH rate _{NPH} = 18.3	IDet	0.946	0.051	452.89	95.62	548.51	2522.15
	NPH insulin	0.896		237.10	183.15	420.96	
<i>ICER</i> Incremental cost-effectiveness ratio, <i>IDet</i> Insulin detemir, <i>NPH</i> Neutral protamine Hagedorn, <i>NSH</i> Non-severe hypoglycemia, <i>QALY</i> Quality-adjusted life year, <i>T1DM</i> Type 1 diabetes mellitus, <i>T2DM</i> Type 2 diabetes mellitus							

ICER Incremental cost-effectiveness ratio, *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *NSH* Non-severe hypoglycemia, *QALY* Quality-adjusted life year, *T1DM* Type 1 diabetes mellitus, *T2DM* Type 2 diabetes mellitus

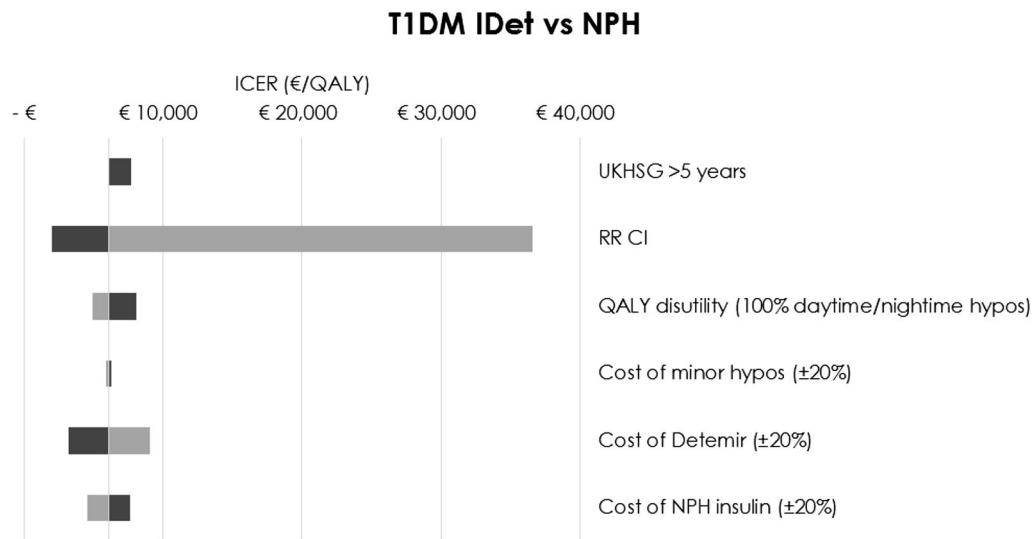


Fig. 1 One-way sensitivity analyses for IDet versus NPH for T1DM in Spain (for NPH non-severe hypoglycemia rate = 35.5). *UKHSG* UK Hypoglycemic Study Group, *RR CI* Rate ratio confidence interval, *ICER* Incremental

cost-effectiveness ratio, *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *QALY* Quality-adjusted life year, *RR* Rate ratio, *T2DM* Type 2 diabetes mellitus

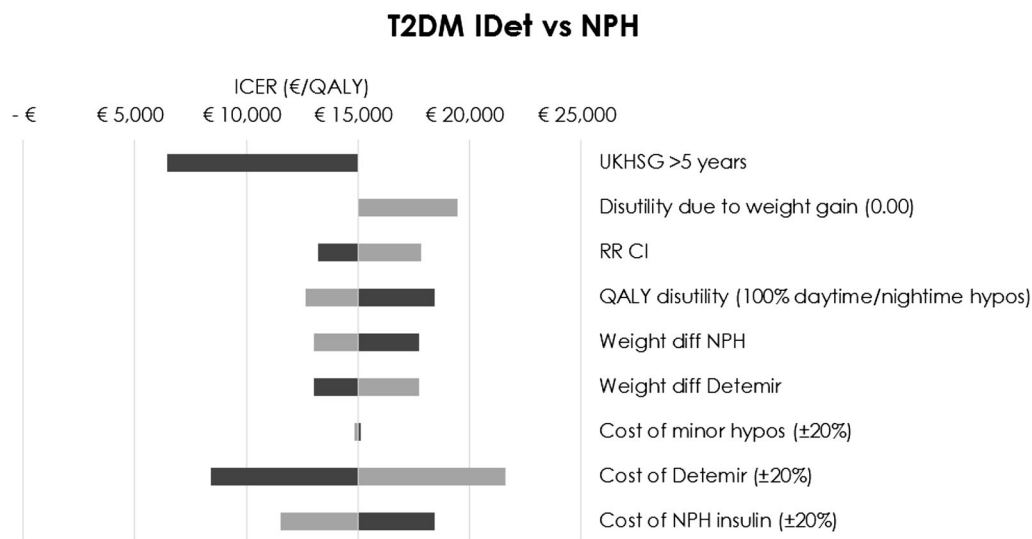


Fig. 2 One-way sensitivity analyses for IDet versus NPH for T2DM in Spain (for NPH non-severe hypoglycemia rate = 4.08). *UKHSG* UK Hypoglycemia Study Group, *RR CI* Rate ratio confidence interval, *ICER* Incremental

cost-effectiveness ratio, *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *QALY* Quality-adjusted life year, *RR* Rate ratio, *T2DM* Type 2 diabetes mellitus

variables have reduced impacts on ICER (Fig. 1). In T2DM, the variable with the highest impact on ICER is IDet cost. When increasing or decreasing it by 20%, the ICER varies between

€8,408/QALY and €21,610/QALY. Disutility due to weight gain is the second most sensitive variable, making the ICER increase to €19,478/QALY when it is not considered. NPH cost

variation ($\pm 20\%$) induces a variation of ICER slightly higher than €5000/QALY. All other variables have a smaller impact on ICER (Fig. 2).

Probabilistic Sensitivity Analysis

Cost-effectiveness acceptability curves allow estimation of the NHS willingness-to-pay for an additional QALY at different ICER thresholds. For the threshold value currently accepted in Spain of €30,000/QALY, IDet has 89.5% and 78.7% probabilities of being cost effective versus NPH for T1DM and T2DM, respectively (Figs. 3, 4).

According to the cost-effectiveness scatterplots, IDet has a 32.9% probability of being more effective and less costly than NPH (dominant) for T1DM (Fig. 5) and 20.7% probability for T2DM (Fig. 6).

DISCUSSION

This direct and transparent short-term CEA was planned to rely on statistically significant

efficacy differences between IDet and NPH; therefore, only non-severe hypoglycemia rates for T1DM and T2DM, and weight gain differences for T2DM were included. The model is based on previously published short-term economical evaluations for Scandinavian countries (Denmark, Finland, the Netherlands, Norway, and Sweden), and, to our knowledge, is the first of its kind in Spain.

This evaluation showed that due to lower hypoglycemic rate and less weight gain, IDet versus NPH insulin is associated with an ICER that stays below the threshold commonly accepted for Spain (€30,000/QALY) [32] both in patients with T1DM and patients with T2DM, and can, therefore, be considered as cost-effective in this country.

In general, the model results are quite robust; in fact, all estimated ICERs in the OWSA remain below the cost-effectiveness acceptability threshold implicitly mentioned above. The only exception is attributing an IDet/NPH hypoglycemia RR close to 1 ($RR = 0.97$; upper extreme of the 95% CI from the CADTH

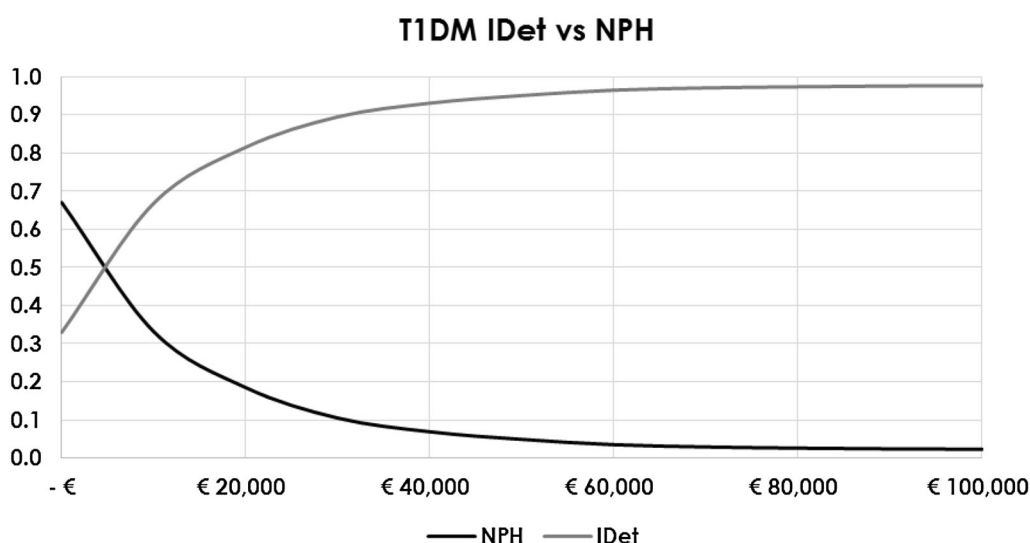


Fig. 3 Cost-effectiveness acceptability curves for IDet versus NPH for T1DM in Spain (for NPH non-severe hypoglycemia rate = 35.5). *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *T1DM* Type 1 diabetes mellitus

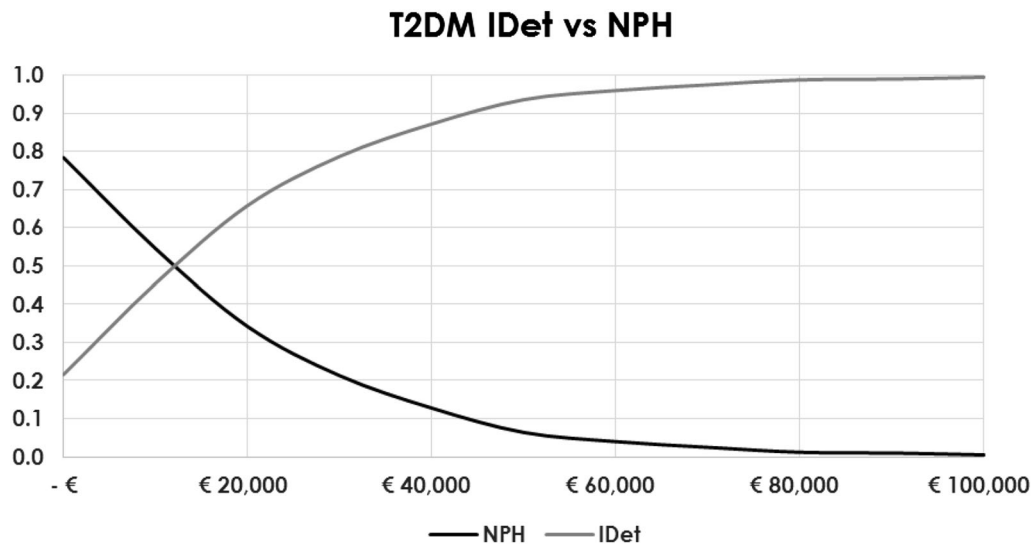


Fig. 4 Cost-effectiveness acceptability curves for IDet versus NPH for T2DM in Spain (for NPH non-severe hypoglycemia rate = 4.08). *IDet* Insulin detemir, *NPH* Neutral protamine Hagedorn, *T2DM* Type 2 diabetes mellitus

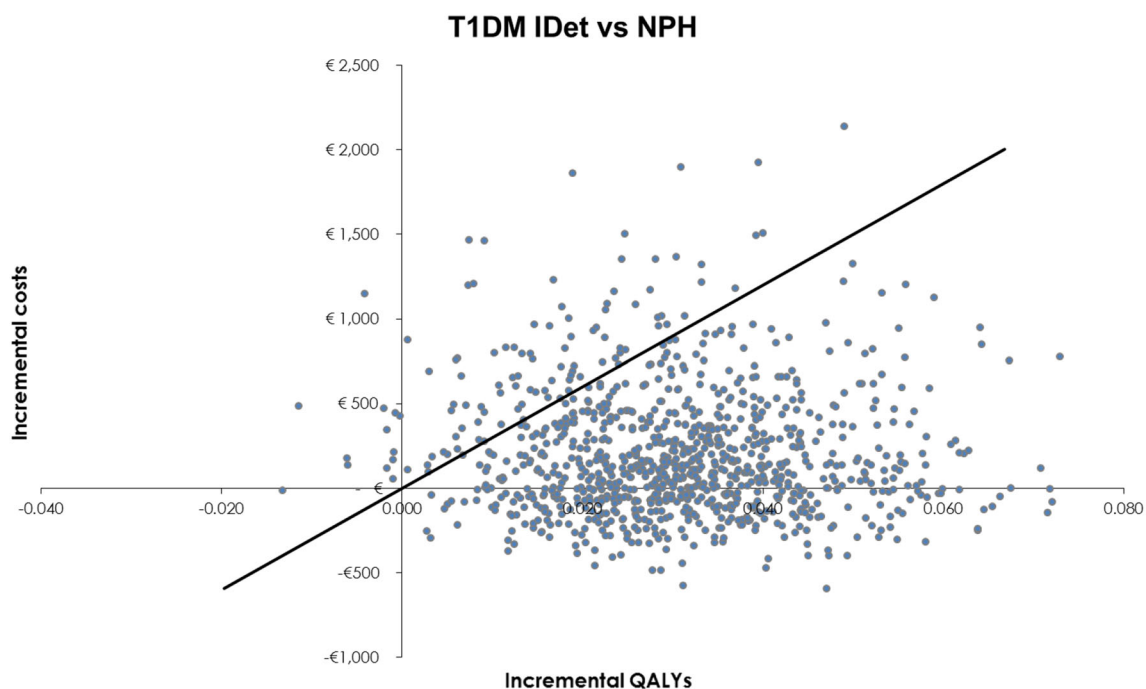


Fig. 5 Cost-effectiveness scatterplot for IDet versus NPH for T1DM in Spain (for NPH non-severe hypoglycemia rate = 35.5). *IDet* Insulin detemir, *NPH* Neutral

protamine Hagedorn, *QALY* Quality-adjusted life year, *T1DM* Type 1 diabetes mellitus

meta-analysis average [21]), for which IDet would not be considered cost-effective with respect to NPH in patients with T1DM. This is

because an RR close to 1 would imply that IDet does not provide any relevant incremental health benefit on hypoglycemia rate versus

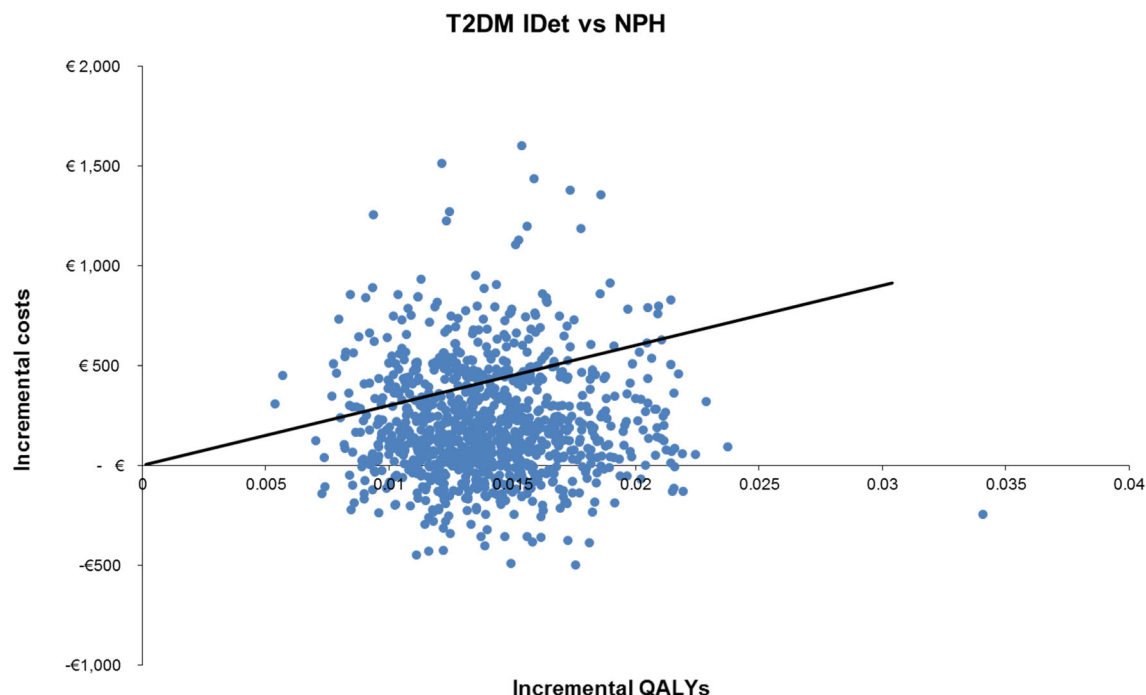


Fig. 6 Cost-effectiveness scatterplot for IDet versus NPH for T2DM in Spain (for NPH non-severe hypoglycemia rate = 4.08). *IDet* Insulin detemir, *NPH* Neutral

protamine Hagedorn, *QALY* Quality-adjusted life year, *T2DM* Type 2 diabetes mellitus

NPH; thus, its higher daily price would not be justified. Another sensitive variable, in both types of diabetes, is the treatment cost. Increasing or decreasing the cost of IDet, makes the ICER vary in an interval up to €6000/QALY wide (T1DM). These estimations are consistent with the structure of the model. Moreover, PSA simulations reveal a probability of cost-effectiveness at a €30,000/QALY threshold of about 90% and 80% in T1DM and T2DM, respectively.

The results of this evaluation must be read in the context of its limitations. First, only the short term is considered. This might underestimate the real clinical benefits of IDet with respect to NPH; in fact, the hypoglycemia rate is expected to increase with treatment duration [33].

With reference to the absolute rate of non-severe hypoglycemia in the NPH

treatment arm, this is a crucial datum that affects the cost-effectiveness of IDet versus NPH for which the three scenarios were estimated in the base-case analysis. The first two scenarios use non-severe hypoglycemia rates coming from the UK Hypoglycemia Study [23] which is a reference observational study for hypoglycemia in diabetic patients. From this study, two non-severe hypoglycemia rates have been selected: one corresponding to patients with recent insulinization (<5 and <2 years for T1DM and T2DM, respectively), and one corresponding to patients with long-run insulinization (>15 and >5 years for T1DM and T2DM, respectively) [23]. The third scenario is based on non-severe hypoglycemia rates from a recently published observational study performed in Spain [24], which should be considered the closest to the “real-world” situation of the Spanish NHS, showing the

highest non-severe hypoglycemia rates. The three scenarios all give cost-effective results and contemplate hypoglycemia rates. It must be considered that the non-severe hypoglycemia rate of these studies was assumed to correspond to treatment with NPH, although insulin type information was not available and most probably included different insulin types. However, this is a conservative assumption in that NPH is known to be associated to higher hypoglycemia rates than more modern insulin analogs [34]. In addition, the use of an overall hypoglycemia RR for IDet versus NPH, instead of a specific RR for non-severe hypoglycemia episodes, due to the lack of a robust source for this datum in the literature, may be considered a limitation of the model. Anyway, the approximated values that are maintained from the original models by Valentine et al. [10] and Ridderstråle et al. [22] give conservative estimations of the non-severe hypoglycemia RR, as already discussed by Valentine et al. [10], and offer the advantage of integrating data from a very controlled setting (RCTs [20, 21]), with a setting that is closer to the “real-world” data (observational study [23]), as explained by Ridderstråle et al. [22].

As the hypoglycemia rate was an overall value (no distinction between nocturnal and diurnal non-severe hypoglycemia events), the utility values associated to diurnal and nocturnal events [17] were averaged to obtain a unique value. However, this simplification was tested in the OWSA by assuming 100% nocturnal or 100% diurnal events and attributing the corresponding utility values. In both ICER estimations, IDet was considered as cost-effective with respect to NPH.

Another limitation may be the use of the WHO DDD of insulin [25]. Even though 40 IU/day is not a “real-world” dose for

patients with diabetes, robust data in this sense are not available due to the dosing variability in clinical practice. Considering all exposed assumptions, this may be considered a conservative estimation.

Long-term cost effectiveness of IDet versus NPH insulin in Spain was previously assessed for basal-bolus therapy, together with four other European countries (Belgium, France, Germany, and Italy) [35]. This evaluation showed that, in the long term, IDet is dominant (in Spain, Belgium, and Germany) or very cost effective (France and Italy) with respect to NPH, due to the reduced cumulative incidence of most diabetes-related complications over the patient lifetime. Other long-term evaluations carried out for Germany, Sweden, and the UK [9, 36–38] have also shown IDet long-term cost effectiveness compared to NPH insulin in both patients with T1DM and patients with T2DM.

However, short-term cost-effectiveness analyses for IDet versus NPH are only available for Scandinavian countries, estimating ICERs in the range of €12,216/QALY to €16,568/QALY (year 2010) for T1DM [10] and €21,768/QALY to €28,349/QALY (year 2012) for T2DM [20] over a 1-year period.

Therefore, a short-term cost-effectiveness estimation was needed in Spain to address the requirements of healthcare decision makers for whom short-term cost effectiveness may be more relevant to immediate budget considerations.

CONCLUSIONS

In conclusion, this analysis shows in a direct manner that IDet can be considered cost-effective with respect to NPH insulin in a Spanish setting for the treatment of both patients with T1DM and patients with T2DM, with ICERs that are in line with or even smaller

than those calculated for other European countries, and in the range commonly accepted for Spain.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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